(7) rejected claims 1-8 under 35 U.S.C. § 112, second paragraph, as being indefinite;

(8) rejected claims 1 and 5 under 35 U.S.C. § 102(b) as being anticipated by Boullier et al., and Koren et al.;

(9) rejected claims 2-4 and 6-8 under 35 U.S.C. § 03(a) as being unpatentable over Boullier et al. and Koren, et al. in view of Kaiserling et al.

By the present amendment, Applicants have amended claims 1-8 and cancelled claims 9-12. Consequently, claims 1-8 currently remain pending. Applicants have elected to prosecute the invention of Group I, namely, the method for detecting LDL and denatured LDL in blood in claims 1-8. Applicants submit a new declaration herewith. The specification has been amended to reflect the claimed benefit of the prior applications. However, no proposed drawing correction will be submitted as discussed below. Applicants acknowledge that the list of references in the specification is not a proper information disclosure statement. No new matter has been added. Entry of this Amendment and early reconsideration of this application are respectfully requested.

The Applicants respectfully submit that the objections to the drawings by the Draftsman are those which cannot be corrected by a proposed drawing correction. The objections are directed to margins, lines, numbers and letters not uniformally thick and well defined, numbers and referenced characters not plain and legible and figure legends poor. Applicants will submit new formal drawings upon issuance of Notice of Allowance.

The Examiner rejected claims 1-8 under 35 U.S.C. § 112, second paragraph, as being indefinite. The applicants respectfully submit that claims 1-8, as now amended, overcome this rejection. Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

The Examiner rejected claims 1 and 5 under 35 U.S.C. § 102(b) as being anticipated by Boullier et al., Clinica Chimica Acta 238, pages 1-10 (1995). This reference teaches the use of an autoantibody or a complex of an autoantibody and LDL as a measuring subject. The first measuring subject is an autoantibody against oxidized LDL, and more specifically an anti-MDA-LDL antibody. The second measuring subject is a complex of native LDL and an autoantibody against it, more specifically a complex of BL3 and LDL. Boullier uses blood taken from an arteriosclerotic patient and measures the above subjects by the ELISA method.

The Applicants respectfully submit that the Examiner's interpretation of Boullier fails to disclose, suggest, teach or show Applicants' invention in amended claims 1 and 5. Applicants' invention measures a complex of oxidized LDL and a reactant, where the reactant is one substance selected from an acute phase reactant, blood coagulation-fibrinolytic related protein and a disinfectant substance produced by macrophages as a measuring subject. Boullier uses a measuring subject which is an autoantibody to oxidized LDL or a complex of native LDL and an autoantibody thereto. The autoantibody in Boullier is an antibody (IgG) while the reactant of the present invention is a protein not containing an antibody. Accordingly, the Examiner will recognize that the two substances are entirely different.

Further, the present invention measures a complex of oxidized LDL and a reactant thereto which is not disclosed, suggested, taught or shown in Boullier. Finally, the present invention uses a measuring subject which is not disclosed, suggested, taught or shown by Boullier. Consequently, Applicants respectfully submit that Boullier does not anticipate claim 1 or 5 and respectfully request that this rejection be withdrawn.

The Examiner rejected claims 1 and 5 under 35 U.S.C. § 102(b) as being anticipated by Koren et al. (WO 96/000903). The Examiner asserts that Koren teaches immunological measuring methods employing monoclonal antibodies to determine apolipoproteins and lipoproteins. Koren discloses, suggests, teaches and shows a method to quickly and reliably determine the concentrations of lipoproteins comprising HDL, LDL and/or apolipoproteins, and their relative ratios. In order to accomplish this method, Koren uses antibodies, namely, monoclonal antibody and recombinant antibody, specifically, immunoreactive to HDL, LDL and apolipoproteins and detexantibody-HDL, antibody-LDL and antibody-apolipoprotein by the ELISA method.

Applicants respectfully submit that the Examiner's interpretation of Koren fails to disclose, suggest, teach or show Applicants' invention in amended claims 1 and 5. Koren discloses, suggests and teaches a measuring subject as a complex selected from those of antibody-HDL, antibody-LDL, and antibody-apolipoprotein. The present invention uses a measuring subject which is a complex of oxidized LDL and a reactant, wherein the reactant is one substance selected from an acute phase

reactant, blood coagulation-fibrinolytic related protein and a disinfectant substance produced by macrophages. Applicants respectfully submit that the oxidized LDL used in the present protein is not disclosed, suggested, or taught from the use of HDL, LDL, and apolipoprotein in Koren as the two groups of substances are entirely different, not related nor obvious in view of one another. Further, Applicants' reactant is a protein which does not contain an antibody, whereas Koren specifically discloses and teaches use of antibodies. Consequently, Applicants respectfully submit the Koren does not anticipate claim 1 or claim 5 and respectfully request that this rejection be withdraw.

The Examiner rejected claims 2-4 and 6-8 under 35 U.S.C. § 103(a) as being unpatentable over Boullier et al. and Koren et al. in view of Kaiserling et al. (Gastroenterology, 1996, Vol. 110, pages 369-374). Applicants respectfully submit that claims 2-4 and 6-8, which depend from independent claim 1, are likewise allowable over Boullier and Koren as discussed above. However, Applicants will address the Examiner's rejection of claims 2-4 and 6-8. The Examiner admits that Boullier and Koren differ from the instant invention in that they fail to teach the specific detection of measuring complexes involving particular acute phase reactants, blood coagulation-fibrinolyitic related proteins or disinfectant produced by macrophages in blood cells. Hence, Boullier and Koren cannot anticipate claims 1 and 5, as amended. The Examiner asserts that Kaiserling teaches several measuring subject complexes that could be utilized in analyzing the morphology and immunophenotype of cells expressing low density lipoprotein LDL and oxidized LDL. In other words, Kaiserling examines

morphologies and immunophenotypes of large number of cells present in the Lipid Islands of human gastric mucosea. Kaiserling observes stained tissues with a light microscope by the munostaining method, using various antibodies to macrophages, smooth muscle cells and lymphocytes. The Lipid Islands consist of foam cells immunoreactive to KP-1 or iM1p, which are all antibodies to macrophages. In cryostat sections, foam cells were thought to contain LDL and oxidized LDL.

Applicant respectfully submit that the Examiner's interpretation of Kaiserling fails to disclose, suggest, teach or show Applicants' invention in amended claims 2-4 and 6-8. Kaiserling teaches that the Lipid Islands of human gastric mucosea consist of foam cells immunoreactive to KP-1, KiM1p, substance as partially overlapping to the reactant of Applicants' invention wherein the reactant is one substance selected from an acute phase reactant, blood coagulation-fibrinolyitic related protein and a disinfectant substance produce by macrophages in the blood. Applicants respectfully submit that it cannot be inferred that oxidized LDL and KP-1 or KiM1p forms a complex because Kaiserling makes no such disclosure, suggestion or teaching. Further, Kaiserling detects the Lipid Islands of human gastric mucosea while the present invention is operative with human blood.

Applicants respectfully submit that there is no motivation for combining Kaiserling, which does not disclose, suggest or teach the presence of protein specifically reactive to oxidize LDL, with Boullier, which does not measure a complex of oxidized LDL and a substance reactive

thereto. Applicants further respectfully submit that there is no motivation for combining Kaiserling, which does not suggest the presence of protein specifically reactive to oxidized LDL, with Koren, which does not measure oxidized LDL. Accordingly, Applicants respectfully submit that the Examiner's asserted interpretation of Boullier or Koren in view of Kaiserling fails to disclosure, suggest, teach or show Applicants' invention of amended claims of 2-4 and 6-8.

For the reasons set forth above it is respectfully requested that the rejection of the claims be withdrawn and the pending claims allowed. A favorable response is earnestly solicited.

Respectfully submitted,

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ATTACHMENT 2

1. A method for detecting **oxidized** LDL **for arteriosclerosis diagnosis characterized in that:** ~~and denatured LDL in blood using as a measuring subject a complex of lower density lipoprotein (LDL) or denatured lower density lipoprotein (denatured LDL: containing oxidized LDL) in which LDL is not oxidatively denatured with~~ **an immunological detecting method is used in which a measuring subject is a complex in blood taken from a human body of oxidized lower density lipoprotein (oxidized LDL)** and one substance selected from ~~an~~ acute phase ~~reactant~~, blood coagulation-fibrinolytic related protein ~~or~~ **and a** disinfectant substance produced by macrophage.

2. The method for detecting **oxidized** LDL **for arteriosclerosis diagnosis** ~~and denatured LDL~~ according to Claim 1, **characterized in that:**

~~using as a measuring subject a complex of~~ an acute phase reactant ~~such as~~ **is selected from** 1-antitrypsin, fibrinogen, fibronectin, lipoprotein (a), C-reactive protein (CRP), Serum amyloid A (SAA), Serum amyloid P component (SAP), 2-macroglobulin, -1antichymotrypsin, 1-acidoglycoprotein, **and a** complement component ~~and the like with LDL or denatured LDL~~.

3. The method for detecting **oxidized** LDL **for arteriosclerosis diagnosis** ~~and denatured LDL~~ according to Claim 1, **characterized in that:**

~~using as a measuring subject a complex of an~~ **blood** coagulation-fibrinolytic related protein ~~such as~~ **is selected from** a tissue factor,

plasminogen, prothrombin, thrombin, antithrombin 3~~,~~ **and a** plasmin activator inhibitor 1~~ and the like with LDL or denatured LDL~~.

4. The method for detecting **oxidized** LDL **for arteriosclerosis diagnosis** ~~and denatured LDL~~ according to Claim 1, **characterized in that:**

~~using as a measuring subject a complex of~~ a disinfectant substance produced by macrophage**s** ~~such as~~ **is selected from** myeloperoxidase, lactoferrin, lysozyme~~,~~ **and** basic protein.

5. The method for detecting **oxidized** LDL **for arteriosclerosis diagnosis** ~~and denatured LDL~~ according to Claim 1, **characterized in that:**

~~using~~ an immunological ~~measuring~~**detecting** method ~~such as~~ **is selected from** an enzyme immunoassay, **a** latex flocculation method, **an** immunological emission spectrochemical analysis~~,~~ **and an** immunochromato method ~~and the like~~.

6. The method for detecting **oxidized** LDL **for arteriosclerosis diagnosis** ~~and denatured LDL~~ according to Claim 2, **characterized in that:**

~~an~~ **said** immunological ~~measuring~~**detecting** method ~~such as~~ **is selected from** an enzyme immunoassay, **a** latex flocculation method, **an** immunological emission spectrochemical analysis~~,~~ **and an** immunochromato method ~~and the like~~.

7. The method for detecting **oxidized** LDL **for arteriosclerosis diagnosis** ~~and denatured LDL~~ according to Claim 3, **characterized in that:**

~~using an~~ **said** immunological ~~measuring~~**detecting** method ~~such as~~ **is selected from** an enzyme immunoassay, **a** latex flocculation method, **an** immunological emission spectrochemical analysis~~,~~ **and an** immunochromato method ~~and the like~~.

8. The method for detecting **oxidized** LDL **for arteriosclerosis diagnosis** ~~and denatured LDL~~ according to Claim 3, **characterized in that:**

~~using an~~ **said** immunological ~~measuring~~**detecting** method ~~such as~~ **is selected from** an enzyme immunoassay, **a** latex flocculation method, **an** immunological emission spectrochemical analysis~~,~~ **and an** immunochromato method ~~and the like~~.

ATTACHMENT 1

1. A method for detecting oxidized LDL for arteriosclerosis diagnosis characterized in that

an immunological detecting method is used in which a measuring subject is a complex in blood taken from a human body of oxidized lower density liloprotein (oxidized LDL) and one substance selected from an acute phase reactant, blood coagulation-fibrinolytic related protein and a disinfectant substance produced by macrophages.

2. The method for detecting oxidized LDL for arteriosclerosis diagnosis according to Claim 1, characterized in that:

an acute phase reactant is selected from α1-antitrypsin, fibrinogen, fibronectin, lipoprotein (a), C-reactive protein (CRP), Serum amyloid A (SAA), Serum amyloid P component (SAP), α2-macroglobulin, α1-antichymotrypsin, α1-acidoglycoprotein and a complement component.

3. The method for detecting oxidized LDL for arteriosclerosis diagnosis according to Claim 1, characterized in that:

blood coagulation-fibrinolytic related protein is selected from a tissue factor, plasminogen, prothrombin, thrombin, antithrombin 3 and a plasmin activator inhibitor 1.

4. The method for detecting oxidized LDL for arteriosclerosis diagnosis according to Claim 1, characterized in that:

a disinfectant substance produced by macrophages is selected from myeloperoxidase, lactoferrin, lysozyme and basic protein.

5. The method for detecting oxidized LDL for arteriosclerosis diagnosis according to Claim 1, characterized in that:

an immunological detecting method is selected from an enzyme immunoassay, a latex flocculation method, an immunological emission spectrochemical analysis and an immunochromato method.

6. The method for detecting oxidized LDL for arteriosclerosis diagnosis according to Claim 2, characterized in that:

said immunological detecting method is selected from an enzyme immunoassay, a latex flocculation method, an immunological emission spectrochemical analysis and an immunochromato method.

7. The method for detecting oxidized LDL for arteriosclerosis diagnosis according to Claim 3, characterized in that:

said immunological detecting method is selected from an enzyme immunoassay, a latex flocculation method, an immunological emission spectrochemical analysis and an immunochromato method.

8. The method for detecting oxidized LDL for arteriosclerosis diagnosis according to Claim 4, characterized in that:

said immunological detecting method is selected from an enzyme immunoassay, a latex flocculation method, an immunological emission spectrochemical analysis and an immunochromato method.